What we claim is:

1. A composition for the burst-free, sustained, programmable release of active material(s) over a period from 1-100 days, which comprises: (1) An active material and (2) A carrier which may contain pharmaceutically-acceptable adjuvant, comprised of a blend of uncapped and end-capped biodegradable-biocompatible copolymer.

2. The composition of Claim 1 wherein the polymeric substance is poly(lactide/glycolide).

3. The composition of Claim 2, wherein the poly(lactide/glycolide) is a blend of uncapped and end-capped forms, in ratios ranging from 100/0 to 1/99.

4. The composition of Claim 3 wherein the copolymer (lactide to glycolide L/G) ratio for uncapped and end-capped polymer is 90/10 to 40/60.

5. The composition of Claim 4 wherein the copolymer (lactide to glycolide L/G) ratio for uncapped and end-capped polymer is 48/52 to 52/48.

6. The composition of Claim 2 wherein the molecular weight of the copolymer is between 2,000-60,000 daltons.

7. The composition of Claim 3 wherein the active material is biologically active agent.

8. The composition of Claim 7 wherein the agent is selected from the group consisting essentially of antibacterial agents; peptides; polypeptides; antibacterial peptides; antimycobacterial agents; antimycotic agents; antiviral agents; antiparastic

agents; antifungal; hormonal peptides; cardiovascular agents; hormonal peptides; cardiovascular agents; narcotic antagonists; analgesics; anesthetics; insulins; steroids including HIV therapeutic drugs (including protease inhibitors) and AZT; estrogens; progestins; gastrointestinal therapeutic agents; non-steroidal anti-inflammatory agents; parasympathoimetic agents; psychotherapeutic agents; tranquilizers; decongestants; sedative-hypnotics; non-estrogenic and non-progestional steroids; sympathomimetic agents; vaccines; vitamins; nutrients; anti-migraine drugs; electrolyte replacements; ergot alkaloids; anti-inflammary agents; prostaglandins; cytotoxic drugs; antigens; antibodies; enzymes; growth factors; immunomodulators; pheromones; prodrugs; psychotropic drugs; nicotine; antiblood clotting drugs; appetite suppressants/stimulants and combinations thereof; contraceptive agents include estrogens such as diethyl silbestrol; 17-beta-estradiol; estrone; ethinyl estradiol; mestranol; progestins such as norethindrone; norgestryl; ethynodiol diacetate; lynestrenol; medroxyprogesterone acetate; dimethisterone; megestrol acetate; chlormadinone acetate; norgestimate; norethisterone; ethisterone; melentate; norgestimate; norethisterone; ethisterone; melengestrol; norethynodrel; and spermicidal compounds such as nonyphenoxypolyoxyethylene glycol; benzethonium chloride; chlorindanol; include gastrointestinal therapeutic agents such as aluminum hydroxide; calcium carbonate; magnesium carbonate; sodium carbonate and the like; non-steroidal antifertility

agents; parasympathomimetic agents; psychotherapeutic agents; major tranquilizers such as chloropromaquine HCL; clozapine; mesoridazine; metiapine; reserpine; thioridazine; minor tranquilizers such as chlordiazepoxide; diazepam; meprobamate; temazepam and the like; rhinological decongestants; sedative-hypnotics such as codeine; phenobarbital; sodium pentobarbital; sodium secobarbital; other steroids such as testosterone and testosterone propionate; sulfonmides; sympathomimetic agents; vaccines; vitamins and nutrient such as the essential amino acids; essential fats; anti-HIV agents; including AZT; antimalarials such as 4-aminoquinolines; 8 aminoquinolines; pyrimethamine; anti-migraine agents such as mazindol; phentermine; anti-Parkinson agents such as L-dopa; antispasmodics such as atropine; methscopolamine bromide; antispasmodics and anticholingeric agents such as bile therapy; digestants; enzymes and the like; antitussives such as dextromethorphan and noscapine; bronchodilators; cardiovascular agents such as anti-hypertensive compounds; Rauwolfia alkaloids; coronary vasodilators; nitroglycerin; organic nitrites; pentaerythriotetranitrate; electrolyte replacements such as potassium chloride; ergotalkaloids such as ergotamine with and without caffein; hydrogenated ergot alkaloids; dihydroergocristine methanesulfate; dihydroergocornine methanesulfonate; dihydroergokroyptine methaneusulfate and combinations thereof; alkaloids such as atropine sulfate; Belladonna; hyoscine hydrobromide; analgesics; narcotics such as

codeine; dihydrocodienone; meperidine; morphine; non-narcotics such as salicylates; aspirin; acetaminophen; and d-propoxyphene; antibiotics such as the cephalosporins including ceflacor and cefuroxime; chloranphenical; gentamicin; Kanamycin A. Kanamycin B; the penicillins; ampicillin; amoxicillin; streptomycin A; antimycin A; chloropamtheniol; metromidazole; oxytetracycline penicillin G; the tetracyclines; including minocycline; fluoro-quinolones including ciprofloxacin; ofoxacin; macrolides including clarithromycin; frythromycin; aminioglycosides including gentamicin; amikacin; tobramycin and kanamycin; beta-lactams including ampacillin; polymyxin-B; amphotercin-B; aztrofonam; chloramphenicol; fusidans; lincosamides; metronidazole; nitro-furantion; imipenem/cilastin; quinolones; systemic antibodies including rifampin; polygenes; sulfunamides; trimethoprim; glycopeptides including vancomycin; teicoplanin and imidazoles; anti-cancer agents; including anti-kaposi's sarcoma; anti-convulsants such as mephenytoin; phenobarbital; trimethadione; anti-emetics such as triethylperazine; antihistamines such as chlorophinazine; dimenhydrinate; diphenhydramine; perphenazine; tripelennamine and the like; anti-inflammatory agents such as hormonal agents; hydrocortisone; prednisolone; prednisone; non-hormonal agents; allopurinol; for claims water-soluble hormone drugs; antibiotics; antitumor agents; anti inflammatory agents; antipyretics; analgesics; antitussives; expectorants; sedatives; muscle relaxants; antiepileptics; anticulcer agents; antidepressants; antiallergic

drugs; cardiotonics; antiarrhythmic drugs; vasodilators; antihypertensives; diuretics; anticoagulants; and antinarcotics; in the molecular wight range of 100-100;000 daltons; indomethacin; phenylbutazone; prostaglandins; cytotoxic drugs such as thiotepa; chloramucil; cyclophosphamide; melphala; nitrogen mustard; methotrexate; antigens such as proteins; glycoproteins; synthetic peptides; carbohydrates; synthetic polysaccharides; lipids; glycolipids; lipopolysaccharides(LPS); synthetic lipopolysaccharides and with or without attached adjuvants such as synthetic muramyl dipeptide derivatives; antigens of such microorganisms as Neisseria gonorrhea; Mycobacterium tuberculosis; Picarinii Pnfumonia; Herpes virus (humonis types 1 and 2); Herpes zoster; Candidia albicans; Candida tropicalis; Trichomonas vaginalis; Haemophilus vaginalis; Group B streptoccoccus ecoli; Microplasma hominis; Hemophilus ducreyi; Granuloma inguimale; Lymphopathia venerum; Treponema palidum; Brucela aborus Brucela meitensis Brucela suis; Brucella canis Campylobacter fetus; Campylobacer fetus intesinalis; Leptospira pomona; Listeria monocytogenes; Brucella ovis; Equine herpes virus 1; Equine arteritis virus; IBR-IBP virus; Chlamydia psittaci; Trichomonas foetus; Taxoplasma gondii; Escherichia coli; Actinobacillus equili; Salmonella abortus ovis. Salmonella abortus eui; Pseudomonas aeruginosa; Corynebacterium equi; Corynebacterium pyogenes; Actinobaccilus seminis; Mycoplasma bovigenitalium; Aspergilus fumigatus; Absidia ramosa; Trypanosoma equiperdum; Babesia cabali; Clostridium tetani;

antibodies which counteract the above microorganisms; and enzymes including ribonuclease; neuramidinase; trypsin; glycogen phosphorylase; sperm lactic dehydrogenase; sp rm hyaluronidase; adenossinetriphosphase; alkaline phosphatase; alkaline phospha esterase; amino peptides; typsin chymotrypsin amylase; muramidase; acrosomal proteinase; diesterase; glutamic acid dehydrogense; succunic and dehydrogenase; beta-glycophosphatase lipase; ATP-ase alpha-peptate gamma-glutamyiotranspeptidase; sterold-beta-ol-dehydrogenase; DPN-di-aprorase; and combinations thereof.

9. The composition of Claim 8 wherein the agent is selected from the group consisting essentially of antibacterial agents; antibacterial peptides; antimycobacterial agents; antimycotic agents; antiviral agents; antiparasitic agents; antifungal; hormonal peptides; cardiovascular agents; narcotic antagonist; analgesics; anesthetics; vaccines; insulins; HIV therapeutic drugs (protease inhibitors); estrogens; progestins; gastrointestinal therapeutic agents; non-steroidal anti-inflammatory agents; parasympathoimetic agents; psychotherapeutic agents; tranquilizers; decongestants; sedative-hypnotics; non-estrogenic and non-progestional steroids; sympathomimetic agents; vaccines; vitamins; nutrients; anti-malarial compounds; anti-migraine drugs; electrolyte replacements; ergot alkaloids; analgetics; non-narcotics; anti-cancer agents; anticonvulsants; anti-emetics; antihistamines; anti-inflammary agents; prostaglandins; cytotoxic drugs; antigens; antibodies; enzymes;

growth factors; immunomodulators; ph romones; prodrugs; psychotropic drugs; appetite suppresants/stimulants; and combinations thereof.

10. The composition of Claim 8 wherein the agent is a peptide or polypeptide.

11. The composition of Claim 10 wherein the agent is a poly peptide.

12. The composition of Claim 11 wherein the molecular weight of the polypeptide is between 1,000-250,000 daltons.

13. The composition of Claim 12 wherein the polypeptide is histatin consisting of 12 amino acids and having a molecular weight of 1563.

14. The composition of Claim 1 characterized by the capacity to completely release histatin in an aqueous physiological environment within from 1 to 40 days with a 100/0 blend of uncapped and end-capped poly(lactide/glycolide) having a L/G ratio of 48/52 to 52/48, and a molecular weight less than 15,000.

15. The composition of Claim 14 wherein the histatin can be completely released within 18 to 40 days and the molecular weight of the poly(lactide/glycolide) is within the range of 28,000 to 40,000.

16. The composition of Claim 2 characterized by the capacity to release up to 90% of the histatin in an aqueous physiological environment from 28-70 days with a 1/99 blend of uncapped and end-capped poly(lactide/glycolide) having a L/G ratio of 48/52 to 52/48 and a molecular weight range of 10,000-40,000 daltons.

17. The composition of Claim 2 characterized by the capacity to release up to 80% of histatin in an aqueous physiological environment from 56-100 days with a 1/99 blend of uncapped and end-capped poly(lactide/glycolide) having a L/G ratio of 75/25 and a molecular weight of less than 15,000 daltons.

18. The composition of Claim 13 having analogs of histatin with chain lengths of from 11-24 amino acids of molecular weights from 1,500-3,000 daltons and characterized by the following structures:

1. D S H A K R H H G Y K R K F H E K H H S H R G Y
2. K R H H G Y K R K F H E K H H S H R G Y R
3. K R H H G Y K R K F H E K H H S R
4. R K F H E K H H S H R G Y R
5. A K R H H G Y K R K F H
6. *A K R H H G Y K R K F H
7. K R H H G Y K R K F

*D-amino acid

19. The composition of Claim 10 wherein the biologically active agent is a polypeptide Leutinizing hormone releasing hormone (LHRH) that is a decapeptide of molecular weight 1182 in its acetate form, and having the structure:

p- E H W S Y G L R P G

20. The composition of Claim 13 having a molecular weight of from 1,000 to 250,000 daltons.

21. The composition of Claim 2 wher in release profiles of variable rates and durations are achieved by blending uncapped and capped microspheres as a cocktail in variable amounts.

22. The composition of Claim 2 wherein release of profiles of variable rates and duration are achieved by blending uncapped and capped polymer in different ratios within the same microspheres.

23. The composition of Claim 12 wherein the entrapped polypeptide is any of the vaccine agents against enterotoxigenic E. coli (ETEC) selected from the group consisting of CFA/I,CFA/II,CS1,CS3,CS6 and CS17, ETEC-related enterotoxins, and combinations thereof.

24. The composition of Claim 23 wherein the entrapped polypeptide consists of peptide antigens of molecular weight range of about 800-5000 daltons for immunization against enterotoxigenic E. coli (ETEC).

25. The composition of Claim 24 wherein the entrapped polypeptide is selected from the group consisting essentially of an antigenic synthetic peptide containing CFA/I pilus protein T-cell epitopes; B-cell epitopes, or mixtures thereof.

26. The composition of Claim 24 wherein the poly(lactide/glycolide) is a blend of uncapped and end-capped forms, in ratios ranging from 48/52 to 52/48.

27. The composition of Claim 7 wherein said agent are selected from the group consisting of water-soluble hormone drugs, antibiotics, antitumor agents, anti inflammatory agents, antipyretics, analgesics antitussives, expectorants, sedatives,

muscle r laxants, antiepileptics, antiulcer agents, antidepressents, antiallergic drugs, cardiotonics, antiarrhythmic drugs, vasodilators, antihypertensiv s, diur tics, anticoagulants, and antinarcotics, in the molecular weight range of 100-100,000 daltons.

28. The composition of Claim 1 wherein said biodegradable poly(lactide/glycolide) is in an oil phase, and is present in about 1-50% (w/w).

29. The composition of Claim 28 wherein concentration of the active agent is in the range of 0.1 to about 60% (w/w).

30. The composition of Claim 29 wherein a ratio of the inner aqueous to oil phases is about 1/4 to 1/40(v/v).

31. The composition of Claim 11 wherein the entrapped polypeptide is active at a low pH, such as LHRH, adrenocorticotropic hormone, epidermal growth factor, calcitonin released polypeptide is bioactive.

32. The composition of Claim 11 when entrapped polypeptide such as histatin is inactive at a low pH, a pH-stabilizing agent of inorganic salts are added to the inner aqueous phase to maintain biological activity of the released peptide.

33. The composition of Claim 11 wherein when entrapped polypeptide such as histatin is inactive at a low pH, a non-ionic surfactant such as polyoxyethylene sorbitan fatty acid esters (Tween 80, Tween 60 and Tween 20) and polyoxyethylene - polyoxypropylene block copolymers (Pluronics) is added to the

inner aqueous phase to maintain biological activity of the released polypeptide.

34. The composition of Claim 32 wherein placebo spheres loaded with the pH-stabilizing agents are coadministered with polypeptide-loaded spheres to maintain the solution pH around the microcapsules and preserve the biological activity of the released peptide in instances where the addition of pH-stablizing agents in the inner aqueous phase is undesirable for the successful encapsulation of the acid pH sensitive polypeptide.

35. The composition of Claim 33 wherein placebo spheres loaded with non-ionic surfactant are coadministered with polypeptide-loaded spheres to maintain biological activity of the released peptide where the addition of non-ionic surfactants in the inner aqueous phase is undesirable for successful encapsulation of the acid pH sensitive polypeptide.

36. The composition of Claim 1 comprising a blend of uncapped and capped polymer, wherein complete solubilization of the copolymer leaves no residual polymer at the site of administration and occurs concurrently with the complete release of the entrapped agent.

37. A process of using composition of Claim 1 for human administration via parenteral routes, such as intramuscular and subcutaneous.

38. A process of using the composition of Claim 1 for human administration via topical route.

39. A process of using the composition of Claim 1 for human administration via oral routes.

40. A proc ss of using the composition of Claim 1 for human administration via nasal, transdermal, rectal, and vaginal routes.

41. A process of using the composition of Claim 1 for human administration in the form of an oral or nasal inhalant for the respiratory tract.

42. A process for preparing controlled release compositions characterized by burst-free, sustained, programmable release of biologically active agents, comprising: dissolving biodegradable poly(lactide/glycolide), in uncapped form in methylene chloride, and dissolving a biologically active agent or active core in water; adding the aqueous layer to the polymer solution and emulsifying to provide an innter water-in-oil (w/o) emulsion; stabilizing the w/o emulsion in a solvent-saturated aqueous phase containing a oil-in-water (o/w) emulsifier; adding said w/o emulsion to an external aqueous layer containing oil-in-water emulsifier to form a ternary emulsion; and stirring the resulting water-in-oil-in-water (w/o/w) emulsion for sufficient time to remove said solvent, and rinsing hardened microcapsules with water and lyophilizing said hardened microcapsules.

43. The process of Claim 42 wherein a solvent-saturated external aqueous phase is added to emulsify the inner w/o emulsion prior to addition of the external aqueous layer, to provide

microcapsules of narrow size distribution range between 0.05-500um.

44. The process of Claim 42 wherein a low temperature of about 0-4 degree C is provided during preparation of the inner w/o emulsion, and a low temperature of about 4-20 degree C is provided during preparation of the w/o/w emulsion to provide a stable emulsion and high encapsulation efficiency.

45. A process for preparing controlled release ~~compositions characterized by burst-free~~, sustained compositions characterized by burst-free, sustained, programmable release of biologically active agents, comprising:

dissolving biodegradble poly(lactide/glycolide) in end-capped form in methylene chloride, and dissolving a biologically active agent or active core in water; adding the aqueous layer to the polymer solution and emulsifying to provide an inner water-in-oil emulsion; stabilizing the w/o emulsion in a solvent-saturated aqueous phase containing a oil-in-water (o/w) emulsifier; adding said w/o emulsion to an external aqueous layer containing oil-in-water emulsifier to form a ternary emulsion; and stirring a resulting water-in-oil-water (w/o/w) emulsion for sufficient time to remove said solvent; and rinsing ~~hardened~~ hardened microcapsules with water; and lyophilizing said hardened microcapsules.

46. The process of Claim 42 wherein a 100/0 blend of uncapped and end-capped polymer is used to provide release of the active core in a continuous and sustained manner without a lag phase.

47. The process of Claim 45 wherein a solvent-saturated external aqueous phase is added to emulsify the inner w/o emulsion prior to addition of the external aqueous layer, to provide microcapsules of narrow size distribution range between 0.05-500um.

48. The process of Claim 45 wherein a low temperature of about 0-4 degree C is provided during preparation of the inner w/o emulsion, and a low temperature of about 4-20 degree C is provided during preparation of the w/o/w emulsion to provide a stable emulsion and high encapsulation efficiency.

49. A method for the protection against infection of a mammal by pathogenic organisms comprising administering orally to said mammal an immunogenic amount of an immunostimulating composition consisting ~~essentially~~ of an antigenic synthetic peptide encapsulated within a poly(lactide/galactide) matrix.

50. The method of Claim 49 wherein the poly(lactide/glycolide) is a blend of uncapped and end-capped forms, in ratios ranging from 100/0 to 1/99.

51. The method of Claim 49 wherein the poly(lactide/glycolide) is a blend of uncapped and end-capped forms in ratios ranging from 90/10 to 40/60.

52. The method of Claim 49 wherein the infection is a bacterial infection.

53. The method of Claim 49 where the synthetic peptide contains an epitope selected from the group consisting of CFA/I pilus protein T-cell epitopes, B-cell epitopes or mixtures thereof.

54. The method of Claim 49 wherein the infection is a viral infection.

55. The method of Claim 49 wherein the inf ction is parasitic infection.

56. The method of Claim 49 wherein the infection is a fungal infection.

57. The method of Claim 52 wherein the bacterial infection is caused by a bacteria selected from the group consisting ~~essentially~~ of Salmonella typhi, Shigella Sonnei, Shigella Flexneri, Shigella dysenteriae, Shigella boydii, Escheria coli, Vibrio cholera, Group D-2, Group E, Group G, Group I, Group 1, Listeria, Erysipelothrix, Mycobacterium, Aerobic pathogenic Actinomycetales, Enterobacteriaceae, Vibrio, aeromonas, Plesiomonas, Helicobacter, W. succinogenes, Acineto bacter spp., Foavobacterium, Pseudomonas, Legionella, Brucella, Haemophilus, Bordetalla, Mycoplasmas, Gardnerella, Streptobacillus, Spirillum, Calymmatobacterium, Clostridium, Treponema, Borrelia, Leptospira, Anaerobic Gram-negative Bacteria including bacilli and Cocci, Anaerobic gram-Positive Nonsporeforming Bacilli and Cocci, yersinia, staphylococcus, clostridium, Enteroccus, Streptoccus, Aerococcus, Planococcus, Stomatococcus, Micrococcus, Lactoccus, Germella, Pediococcus, Leuconostoc, Bacillus, Neisseria, Branhamella, Coryne bacterium, campylobacter, Arcanobacterium haemolyticum, Rhodococcus spp.. Rhodococcus, Group A-4.

58. The method in accordance with Claim 49 comprising administering orally to said mammal an immunogenic amount of a

pharmaceutical composition consisting ~~essentially~~ of an antigenic synthetic peptide in the amount of .1 to 1%.

59. A vaccine for the immunization of a mammal against infection caused by pathogenic organisms prepared from the ~~composition~~ formulation of Claim 57.

60. The vaccine according to Claim 59 wherein the polymeric substance is poly(DL-lactide-co-glycolide).

61. The vaccine according to Claim 60 wherein the relative ratio between the lactide and glycolide (L/G) component is within the range of 40/60 to 0/100.

62. The vaccine according to Claim 61 wherein the relative ratio between the amount of lactide and glycolide component is within the range of 90/10 to 40/60.

63. A vaccine according to Claim 62 wherein the pathogenic organisms are bacterial.

64. A vaccine according to Claim 62 wherein the pathogenic organisms are viral.

65. A vaccine according to Claim 62 wherein the pathogenic organisms are fungal.

66. A vaccine according to Claim 62 wherein the pathogenic organisms are parasitic.

67. The vaccine according to Claim 63 wherein the antigenic synthetic peptide is selected from the group consisting essentially of Synthetic Peptides Containing CFA/I Pilus Protein T-cell Epitopes (Starting Sequence # given)

4(Asn-Ile-Thr-Val-Thr-Ala-Ser-Val-Asp-Pro),

8(Thr-Ala-Ser-Val-Asp-Pro-Val-Ile-Asp-Leu),

12(Asp-Pro-Val-Ile-Asp-Leu-Leu-Gln-Ala-Asp),

15(Ile-Asp-Leu-Leu-Gln-Ala-Asp-Gly-Asn-Ala),

20(Ala-Asp-Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val),

26(Pro-Ser-Ala-Val-Lys-Leu-Ala-Tyr-Ser-Pro),

72(Leu-Asn-Ser-Thr-Val-Gln-Met-Pro-Ile-Ser),

78(Met-Pro-Ile-Ser-Val-Ser-Trp-Gly-Gly-Gln),

87(Gln-Val-Leu-Ser-Thr-Thr-Ala-Lys-Glu-Phe),

126(Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr), and

133(Gly-Asn-Tyr-Ser-Gly-Val-Val-Ser-Leu-Val), and

mixtures thereof;

Synthetic Peptides Containing CFA/I Pilus Protein B-cell (antibody) Eptiopes (Starting Sequence # given)

3(Lys-Ana-Ile-Thr-Val-Thr-Ala-Ser-Val),

11(Val-Asp-Pro-Val-Idle-Asp-Leu-Leu-Gln-Ala-Asp),

22(Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val),

32(Ala-Tyr-Ser-Pro-Ala-Ser-Lys-Thr-Phe-Lys-Thr-Phe-Glu-Ser-Tyr-Arg-Val),

32(Ala-Tyr-Ser-Pro-Ala-Ser-Lys-Thr-Phe),

38(Lys-Thr-Phe-Glu-Ser-Tyr-Arg-Val),

66(Pro-Gln-Leu-Thr-Asp-Val-Leu-Asn-Ser),

93(Ala-Lys-Glu-Phe-Glu-Ala-Ala-Ala),

124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr),

127(Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and

124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and mixtures thereof; and

Synthetic Peptides Containing CFA/I Pilus Protein T-cell and B-cell (antibody) Epitopes (Starting Sequence # given)

3(Lys-Asn-Ile-Thr-Val-Thr-Ala-Ser-Bal-Asp-Pro),

8(Thr-Ala-Ser-Bal-Asp-Pro-Bal-Ile-Asp-Leu-Leu-Gln-Ala-Asp),

11(Bal-Asp-Pro-Bal-Ile-Asp-Leu-Leu-Gln-Ala-Asp),

20(Ala-Asp-Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val),

124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and

126(Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and mixtures thereof.

68. The vaccine according to Claim 67 wherein the bacteria is selected from the group consisting ~~essentially~~ of Salmonella typhi, Shigella Sonnei, Shigella Flexneri, Shigella dysenteriae, Shigella boydii, Escheria coli, Vibrio cholera, Group D-2, Group E, Group G, Group I, Group 1, Listeria, Erysipelothrix, Mycobacterium, Aerobic pathogenic Actinomycetales, Enterobacteriaceae, Vibrio, aeromonas, Plesiomonas, Helicobacter, W. succinogenes, Acineto bacter spp., Foavobacterium, Pseudomonas, Legionella, Brucella, Haemophilus, Bordetalla, Mycoplasmas, Gardnerella, Streptobacillus, Spirillum, Calymmatobacterium, Clostridium, Treponema, Borrelia, Leptospira, Anaerobic Gram-negative Bacteria including bacilli and Cocci, Anaerobic gram-Positive Nonsporeforming Bacilli and Cocci, yersinia, staphylococcus, clostridium, Enteroccus, Streptoccus, Aerococcus, Planococcus, Stomatococcus, Micrococcus, Lactoccus,

Germella, Pediococcus, Leuconostoc, Bacillus, Neisseria, Branhamella, Coryne bacterium, campylobacter, Arcanobacterium haemolyticum, Rhodococcus spp.. Rhodococcus, Group A-4.

69. The vaccine according to Claim 67 wherein the antigenic synthetic peptide is selected from the group consisting ~~essentially~~ of 4(Asn-Ile-Thr-Val-thr-Ala-Ser-Val-Asp-Pro), 8(Thr-Ala-Ser-Val-Asp-Pro-Val-Ile-Asp-Leu), 12(Asp-Pro-Val-Ile-Asp-Leu-Leu-Gln-Ala-Asp), 15(Ile-Asp-Leu-Leu-Gln-Ala-Asp-Gly-Asn-Ala), 20(Ala-Asp-Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val), 26(Pro-Ser-ala-Val-Lys-Leu-Ala-Tyr-Ser-Pro), 72(Leu-Asn-Ser-Thr-Val-Gln-Met-Pro-Ile-Ser), 78(Met-Pro-Ile-Ser-Val-Ser-Trp-Gly-Gly-Gln), 87(Gln-Val-Leu-Ser-Thr-Thr-Ala-Lys-Glu-Phe), 126(Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr), and 133(Gly-Asn-Tyr-Ser-Gly-Val-Val-Ser-Leu-Val), and mixtures thereof.

70. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 4(Asn-Ile-Thr-Val-Thr-Ala-ser-Val-Asp-Pro).

71. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 8(Thr-ala-ser-Val-Asp-Pro-Val-Ile-asp-Leu).

72. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 12(Asp-Pro-Val-Ile-Asp-Leu-Leu-Gln-Ala-Asp).

73. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 15(Ile-Asp-Leu-Leu-Gln-Ala-Asp-Gly-Asn-Ala).

74. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 20(Ala-Asp-Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val).

75. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 26(Pro-Ser-Ala-Val-Lys-Leu-Ala-tyr-Ser-Pro).

76. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 72(Leu-Asn-Ser-Thr-Val-Gln-Met-Pro-Ile-Ser).

77. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 78(Met-Pro-Ile-Ser-Val-Ser-Trp-Gly-Gly-Gln).

78. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 87(Gln-Val-Leu-Ser-Thr-thr-Ala-Lys-Glu-Phe).

79. The vaccine according to claim 69 wherein the antigenic synthetic peptide is 126(Ala-Gly-Thr-Ala-pro-Thr-Ala-Gly-Asn-Tyr).

80. The vaccine according to Claim 69 wherein the antigenic synthetic peptide is 133(Gly-Asn-Tyr-Ser-Gly-Val-Val-Ser-Leu-Val).

81. The vaccine according to Claim 67 wherein the antigenic synthetic peptide is selected from the group consisting ~~essentially~~ of 3(Lys-Ana-Ile-Thr-Val-Thr-Ala-Ser-Val),
11(Val-Asp-Pro-Val-Ile-Asp-Leu-Leu-Gln-Ala-Asp),
22(Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val),
32(Ala-Tyr-Ser-Pro-Ala-Ser-Lys-Thr-Phe-Lys-Thr-Phe-Glu-Ser-Tyr-Arg-Val),
32(Ala-Tyr-Ser-Pro-Ala-Ser-Lys-Thr-Phe),
38(Lys-Thr-Phe-Glu-Ser-Tyr-Arg-Val),
66(Pro-Gln-Leu-Thr-Asp-Val-Leu-Asn-Ser),
93(Ala-Lys-Glu-Phe-Glu-Ala-Ala-Ala),
124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr),
127(Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and
124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and mixtures thereof.

82. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 3(Lys-Ana-Ile-Thr-Val-Thr-Ala-Ser-Val).

83. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 11(Val-Asp-Pro-Val-Ile-Asp-Leu-Leu-Gln-Ala-Asp).

84. The vaccine according to Claim 81 wherein the antigenic synthetic peptid is 22(Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val).

85. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 32(Ala-Tyr-Ser-Pro-Ala-Ser-Lys-Thr-Phe-Lys-Thr-Phe-Glu-Ser-Tyr-Arg-Val).

86. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 32(Ala-Tyr-Ser-Pro-Ala-Ser-Lys-Thr-Phe).

87. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 38(Lys-Thr-Phe-Glu-Ser-Tyr-Arg-Val).

88. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 66(Pro-Gln-Leu-Thr-Asp-Val-Leu-Asn-Ser).

89. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 93(Ala-Lys-Glu-Phe-Glu-Ala-Ala-Ala).

90. The vaccine according to Claim 81 wherein the antigenic synthetic peptide is 124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr).

91. The vaccine according to Claim 82 wherein the antigenic synthetic peptide is 127(Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser).

92. The vaccine according to Claim 82 wherein the antigenic synthetic peptide is 124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser).

93. The vaccine according to Claim 67 wherein the antigenic synthetic peptide is selected from the group consisting ~~essentially~~ of 3(Lys-Asn-Ile-Thr-Val-Thr-Ala-Ser-Bal-Asp-Pro), 8(Thr-Ala-Ser-Bal-Asp-Pro-Bal-Ile-Asp-Leu-Leu-Gln-Ala-Asp), 11(Bal-Asp-Pro-Bal-Ile-Asp-Leu-Leu-Gln-Ala-Asp),

20(Ala-Asp-Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val), 124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and 126(Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser), and mixtures thereof.

94. The vaccine according to Claim 93 wherein the antigenic synthetic peptide is 3(Lys-Asn-Ile-Thr-Val-Thr-Ala-Ser-Bal-Asp-Pro).

95. The vaccine according to Claim 93 wherein the antigenic synthetic peptide is 8(Thr-Ala-Ser-Bal-Asp-Pro-Bal-Ile-Asp-Leu-Leu-Gln-Ala-Asp).

96. The vaccine according to Claim 93 wherein the antigenic synthetic peptide is 11(Bal-Asp-Pro-Bal-Ile-Asp-Leu-Leu-Gln-ala-Asp).

97. The vaccine according to Claim 93 wherein the antigenic synthetic peptide is 20(Ala-Asp-Gly-Asn-Ala-Leu-Pro-Ser-Ala-Val).

98. The vaccine according to Claim 93 wherein the antigenic synthetic peptide is 124(Lys-Thr-Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser).

99. The vaccine according to Claim 93 wher in the antigenic synthetic peptide is 126(Ala-Gly-Thr-Ala-Pro-Thr-Ala-Gly-Asn-Tyr-Ser).

100. The method of Claim 54, wherein the viral infection is caused by a virus selected from the group consisting ~~essentially~~ of hepatitis A, hepatitis B, hepatitis C, Varicella-Zoster virus, Epstein-Barr virus, Rotaviruses, polio virus, human immunodeficiency virus (HIV), herpes simplex virus type 1, human retroviruses, herpes simplex virus type 2, Ebola virus, cytomegalo viruses, Herpes Simplex viruses, Human cytomegalovirus, Varicella-Zoster Virus, Epstein-Barr Virus, Poxvirus, Influenza viruses, Parainfluenza viruses, Respiratory Syncytial virus, Rhinoviruses, Coronaviruses, Adenoviruses, Measles virus, Mumps virus, Robella Virus, Human Parvoviruses, Arboviruses, Rabies virus, Enteroviruses, reoviruses, Viruses Causing gastroenteritis Hepatitis Viruses, Filoviruses, Arenaaviruses, Papillomaviruses, Polyomaviruses, Human Immunodeficiency viruses, Human Retroviruses, and Spongiform Encephalopathies.

101. The method in accordance with Claim 49 comprising administering orally to said mammal an immunogenic amount of a pharmaceutical composition consisting ~~essentially~~ of an antigen in the amount of .1 to 1%.

102. A vaccine for the immunization of a mammal against infection by pathogenic organisms consisting ~~essentially~~ of an antigen in the amount of 0.1 to 1% ~~en~~capsulated within a biodegradable-biocompatible polymeric poly(DL-lactide-co-glycolide) matrix wherein the polymer is end-capped or a blend of uncapped and end-capped polymers.

103. The vaccine according to Claim 100 wherein the polymer is a blend of end-capped and uncapped polymers.

104. The vaccine according to Claim 103 wherein the relative ratio between the lactide and glycolide component is within the range of 90/10 to 40/60.

105. The vaccine according to Claim 103 wherein the relative ratio between the amount of lactide and glycolide component is within the range of 48/52 to 52/48.

106. The vaccine according to Claim 102 wherein the antigen is a bacteria or derivatives thereof.

107. The vaccine according to Claim 103 wherein the antigen is a virus or derivatives thereof.

108. The vaccine according to Claim 103 wherein the antigens is a parasite or derivative thereof.

109. The vaccine according to Claim 103 wherein the antigen is a fungus or derivative thereof.

110. The vaccine according to Claim 106 wherein the bacteria is selected from the group consisting ~~essentially~~ of Salmonella typhi, Shigella Sonnei, Shigella Flexneri, Shigella dysenteriae, Shigella boydii, Escheria coli, Vibrio cholera, Group D-2, Group E, Group G, Group I, Group 1, Listeria, Erysipelothrix, Mycobacterium, Aerobic pathogenic Actinomycetales, Enterobacteriaceae, Vibrio, aeromonas, Plesiomonas, Helicobacter, W. succinogenes, Acineto bacter spp., Foavobacterium, Pseudomonas, Legionella, Brucella, Haemophilus, Bordetalla, Mycoplasmas, Gardnerella, Streptobacillus, Spirillum, Calymmatobacterium, Clostridium, Treponema, Borrelia, Leptospira, Anaerobic Gram-negative Bacteria including bacilli and Cocci, Anaerobic gram-Positive Nonsporeforming Bacilli and Cocci, yersinia, staphylococcus, clostridium, Enteroccus, Streptoccus, Aerococcus, Planococcus, Stomatococcus, Micrococcus, Lactoccus, Germella, Pediococcus, Leuconostoc, Bacillus, Neisseria, Branhamella, Coryne bacterium, campylobacter, Arcanobacterium haemolyticum, Rhodococcus spp.. Rhodococcus, Group A-4.

111. The vaccine of Claim 107 wherein the virus is selected from the group consisting ~~essentially~~ of hepatitis A, hepatitis B, hepatitis C, Varicella-Zoster virus, Epstein-Barr virus, Rotaviruses, polio virus, human immunodeficiency virus (HIV),

herpes simplex virus typ 1, human retroviruses, herpes simplex virus type 2, Ebola virus, cytomegalo viruses, Herpes Simplex viruses, Human cytomegalovirus, Varicella-Zoster Virus, Epstein-Barr Virus, Poxvirus, Influenza viruses, Parainfluenza viruses, Respiratory Syncytial virus, Rhinoviruses, Coronaviruses, Adenoviruses, Measles virus, Mumps virus, Robella Virus, Human Parvoviruses, Arboviruses, Rabies virus, Enteroviruses, reoviruses, Viruses Causing gastroenteritis Hepatitis Viruses, Filoviruses, Arenaaviruses, Papillomaviruses, Polyomaviruses, Human Immunodeficiency viruses, Human Retroviruses, and Spongiform Encephalopathies.

112. An immunostimulating composition comprising encapsulating-microspheres, which may contain a pharmaceutically-acceptable adjuvant, wherein said microspheres having a diameter between 1 nanogram (ng) to 10 microns (um) are comprised of (a) a biodegradable-biocompatible poly (DL-lactide-co-glycolide) as the bulk matrix, wherein the copolymer (lactide to glycolide L/G) ratio for uncapped and end-capped polymer is ~~0/100 to 1/99~~ 1/100 to 99/1 and (b) an immunogenic substance comprising a bacteria, virus, fungus, parasite, or derivative thereof, that serves to elicit the production of antibodies in animal subjects.

113. An immunostimulating composition according to Claim 112 wherein the amount of said immunogenic substance is within the range of 0.1 to 1.5% based on the volume of said bulk matrix.

114. An immunostimulating composition according to Claim 10 wherein the immunogenic substance comprises Colony Factor Antigen (CFA/II), hepatitis B surface antigen (HBsAg), a mixture thereof physiologically similar antigen.

115. An immunostimulating composition according to Claim 113 wherein the relative ratio between the lactide and glycolide component is within the range of 48/52 to 52/48.

116. An immunostimulating composition according to Claim 113 wherein the size of more than 50% of said microspheres is between 5 to 10 um in diameter by volume.

117. An immunostimulating composition according to Claim 113 wherein the immunogenic substance is the synthetic peptide representing the peptide fragment beginning with the amino acid residue 63 through 78 of Pilus Protein CS3, said residue having the amino acid sequence, 63(Ser-Lys-Asn-Gly-Thr-Val-Thr-Try-Ala-His-Glu-Thr-Asn-Asn-Ser-Ala).

118. A vaccine comprising an immunostimulating composition of Claim 113 and a sterile, pharmaceutically-acceptable carrier therefor.

119. A vaccine comprising an immunostimulating composition of Claim 118 wherein said immunogenic substance is Colony Factor Antigen (CFA/II).

120. A vaccine comprising an immunostimulating composition of Claim 119 wherein said immunogenic substance is hepatitis B surface antigen (HBsAg).

121. A method for the vaccination against bacterial infection comprising administering to a human, an antibactericidally effective amount of a composition of Claim 118.

122. A method according to Claim 121 wherein the bacterial infection is caused by a bacteria selected from the group consisting ~~essentially~~ of Salmonella typhi, Shigella Sonnei, Shigella Flexneri, Shigella dysenteriae, Shigella boydii, Escheria coli, Vibrio cholera, Group D-2, Group E, Group G, Group I, Group 1, Listeria, Erysipelothrix, Mycobacterium, Aerobic pathogenic Actinomycetales, Enterobacteriaceae, Vibrio, aeromonas, Plesiomonas, Helicobacter, W. succinogenes, Acineto bacter spp., Foavobacterium, Pseudomonas, Legionella, Brucella, Haemophilus, Bordetalla, Mycoplasmas, Gardnerella, Streptobacillus, Spirillum, Calymmatobacterium, Clostridium, Treponema, Borrelia, Leptospira, Anaerobic Gram-negative Bacteria including bacilli and Cocci, Anaerobic gram-Positive Nonsporeforming Bacilli and Cocci, yersinia, staphylococcus,

clostridium, Enteroccus, Streptoccus, Aerococcus, Planococcus, Stomatococcus, Micrococcus, Lactoccus, Germella, Pediococcus, Leuconostoc, Bacillus, Neisseria, Branhamella, Coryne bacterium, campylobacter, Arcanobacterium haemolyticum, Rhodococcus spp.. Rhodococcus, Group A-4.

123. A method for the vaccination against viral infection comprising administering to a human an antivirally effective amount of a composition of Claim 108.

124. A diagnostic assay for bacterial infections comprising a composition of Claim 7.

125. A method of preparing an immunotherapeutic agent against infections caused by a bacteria comprising the steps of (1) immunizing a plasma donor with a vaccine according to Claim 52 such that a hyperimmune globulin is produced which contains antibodies directed against the bacteria; (2) separating the hyperimmune globulin and (3) purifying the hyperimmune globulin.

126. A method preparing an immunotherapeutic agent against infections caused by a virus comprising the step of immunizing a plasma donor with a ~~vaccine~~ immunostimulating composition according to Claim ~~126~~ 125 such that hyperimmune globulin is produced which contains antibodies directed against the hepatitis B virus.

127. An immunotherapy method comprising the step of administering to a subject an immunostimulatory amount of hyperimmune globulin prepared according to Claim 125.

128. An immunotherapy method comprising the step of administering to a subject an immunostimulatory amount of hyperimmune globulin prepared according to Claim 125.

129. A method for the protection against infection of a subject by enteropathogenic organisms or hepatitis B virus comprising administering to said subject an immunogenic amount of an immunostimulating composition of Claim 112.

130. A method according to Claim 127 wherein the immunostimulating composition is administered orally.

131. A method according to Claim 127 wherein the immunostimulating composition is administered parenterally.

132. A method according to Claim 127 wherein the immunostimulating composition is administered in four separate doses on day 0, day 7, day 14, and day 28.

133. A method according to Claim 114 wherein the immunogenic substance is the synthetic peptide representing the peptide fragment beginning with the amino acid residue 63 through 78 of

Pilus Protein CS3 said residue having the amino acid sequence 63(Ser-Lys-Asn-Gly-Thr-Val-Thr-Try-ala-His-Glu-thr-asn-Asn-Ser-Ala).

134. A method for the protection against or therapeutic treatment of bacterial infection in the soft tissue or bone of a mammal comprising administering locally to said mammal a bactericidally-effective amount of a composition of Claim 2, wherein the active material is an antibiotic which is controlled release within a period of about 1 to 100 days.

135. The method according to Claim 134 wherein the biodegradable poly(DL-lactide-co-glycolide) is a blend of uncapped and end-capped forms having a relative ratio between the amount of lactide and glycolide component within the range of 100/0 to 1/99.

136. A method according to Claim 135 wherein the bacterial infection is (1) a subcutaneous infection secondary to contaminated abdominal surgery, (2) an infection surrounding prosthetic devices and vascular grafts, (3) ocular infections, (4) topical skin infections, (5) orthopedic infections, including osteomyelitis, and (6) oral infections.

137. The method according to Claim 136 wherein the oral infections are pericoronitis or periodontal disease.

138. The method according to Claim 135 wherein the administration is effected prior to infection.

139. The method according to Claim 135 wherein the administration is effected subsequent to infection.

140. The method according to Claim 135 wherein said animal is a human.

141. The method according to Claim 135 wherein said animal is a nonhuman.

142. The method in accordance with Claim 135 comprising applying to the soft tissue or bone tissue of said animal a bactericidally-effective amount of ~~a pharmaceutical composition consisting essentially of an antibiotic in the ant~~ said antibiotic, selected from the group consisting of a beta-lactam, aminoglycolide, polymyxin-b, Amphotericin B, Aztreonam, cephalosporins, chloramphenicol, fusidans, lincosamides, macrolides, methronidazole, nitro-furation, Imipenem/cilastin, quinolones, refampin, polyenes, tetracycline, sulfonamides, trimethoprim, vancomycin, teicoplanin, imidazoles, and erythromycin, encapsulated within a biodegradable poly(DL-lactide-co-glycolide) polymeric matrix, wherein the amount of the lactide and glycolide (L/G) component is within the range of 48/52 to 52/48 based on the weight of said polymeric matrix which is present in the amount of from 40 to 95

percent, resulting in the controlled release of a bact riacidal amount of the said antibiotic over a period of from 1 to 100 days.

143. The method of Claim 142 wherein the polymeric matrix consists ~~essentially~~ of a poly(DL-lactide-co-glycolide) wherein the relative ratio between the amount of lactide and glycolide (L/G) component is within the range of 48/52 to 52/48.

144. The method of Claim 142 wherein the bacterial infection is caused by a resistant or non-resistant bacteria selected from the group consisting ~~essentially~~ of Enterobacteriaceae; Klebsiella sp.; Bacteroides sp. Enterococci; Proteus sp.; Streptococcus sp.; Staphylococcus sp.; Pseudomonas sp.; Neisseria sp.; Pedptostreptococcus sp.; Fusobacterium sp.; Actinomyces sp.; Mycobacterium sp.; Listeria sp.; Corynebacterium sp.; Proprionibacterium sp.; Actinobacillus sp.; Aerobacter sp.; Borrelia sp.; Campylobacter sp.; cytophaga sp.; Pasteurella sp.; Clostridium sp., Enterobacter aerogenes, Peptococcus sp., Proteus vulgaris, Proteus morganii, Staphylococcus aureus, Streptococcus pyogenes, Actinomyces sp., Campylobacter fetus, and Legionella pneumophila, ampillin-resistant strain of S. aureus, and methicillin-resistant strain of S. aureus.

145. The method of Claim 142 wherein the antibiotic is selected from the group consisting ~~essentially~~ of a beta-lactam,

aminoglycolide, polymyxin-B, amphotericin B, aztreonam, cephalosporins, chloramphenicol, fusidans, lincosamides, macrolides, methronidazole, nitro-furantoin, Imipenem/cilastin, quinolones, rifampin, polyenes, tetracycline, sulfonamides, trimethoprim, vancomycin, teicoplanin, imidazoles, and erythromycin.

146. The method of Claim 145 wherein the beta-lactam is cephalosporin.

147. The method of Claim 145 wherein the beta-lactam is penicillin.

148. The method of Claim 145 wherein the aminoglycolide is gentamicin.

149. The method of Claim 145 wherein the aminoglycolide is amikacin.

150. The method of Claim 145 wherein the aminoglycolide is tobramycin.

151. The method of Claim 145 wherein the aminoglycolide is kanamycin.

152. The method of Claim 145 wherein the beta-lactam is an ampicillin.

153. The method of Claim 152 wherein the polymeric matrix consists ~~essentially~~ of a poly(DL-lactide-co-glycolide) wherein the relative ratio between the amount of lactide and glycolide (L/G) component is within the range of 48/52 to 58/42.

154. The method of Claim 152 wherein the ampicillin is present in an amount of from 5 to 60 percent and the amount of polymeric matrix is from 40 to 95 percent.

155. The process ~~of using the composition of~~ Claim 1 to treat humans ~~in need, thereof~~, suffering from diseases and/or ailments from the group consisting of: viral infections; bacterial infections; fungal infections; parastic infections and more specific diseases and/or ailments; such as as, aids; alzheimer's dementia; angiogenesis diseases; aphthour ulcers in AIDS patients; asthma; atopic dermatitis; psoriasis; basal cell carcinoma; benign prostatic hypertrophy; blood substitute; blood substitute in surgery patients; blood substitute in trauma patients; breast cancer; breast cancer; cutaneous & metastatic; cachexia in AIDS; campylobacter infection; cancer; pnemonia; sexually transmitted diseases (STDs); cancer; viral dieases; candida albicians in AIDS and cancer; candidiasis in HIV infection; pain in cancer; pancreatic canc r; parkinson's

disease; peritumoral brain edema; postoperative adhesions (prevent); proliferative diseases; prostate cancer; ragweed allergy; renal disease; rest nosis; rheumatoid arthritis; rheumatoid arthritis; allergies; rotavirus infection; scalp psoriasis; septic shock; small-cell lung cancer; solid tumors; stroke; thrombosis; type I diabetes; type I diabetes w/kidney transplants; type II diabetes; viseral leishmaniasis; malaria; periodontal or gum disease; cardiac rthythm disorders; central nervous system diseases; central nervous system disorders; cervical dystonia (spasmodic torticollis); choridal neovascularization; chronic hepatitis c, b and a; colitis associated with antibiotics; colorectal cancer; coronary artery thrombosis; cryptosporidiosis in AIDS; cryptosporidium parvum diarrhea in AIDS; cystic fibrosis; cytomegalovirus disease; depression; social phobias; panic disorder; diabetic complications; disabetic eye disease; diarrhea associated with antibiotics; erectile dysfunction; genital herpes; graft-vs host disease in transplant patients; growth hormone deficiency; head and neck cancer; head trauma; stroke; heparin neutralization after cardiac bypass; hepatocellular carcinoma; HIV; HIV infection; huntington's disease; CNS diseases; hypercholesterolemia; hypertension; inflammation; inflammation and angiogensis; inflammation in cardiopulmonary bypass; influenza; migrain head ache; interstitial cystitis; kaposi's sarcoma; kaposi's sarcoma in AIDS; lung cancer; melanoma; molluscum contagiosum in AIDS; multiple sclerosis; neoplastic

meningitis from solid tumors; non-small cell lung cancer; organ transplant rejection; osteoarthritis; rheumatoid arthritis; osteoporosis; drug addiction; shock; ovarian cancer; Amebiasis; Babesiasis; Chagas' disease (Trypanosoma cruzi); Cryptosporidiosis; Cysticercosis; Fascioliasis; Filariasis; Echinococcosis; Giardiasis; Leishmaniasis; Malaria; Paragonimiasis; Pneumocystosis; Schistosomiasis; Strongylodiasis; Toxocariasis; Toxoplasmosis; Trichinellosis; Trichomoniasis; yeast infection; and pain.

156. A vaccine for prepared from the composition of Claim 1 to prevent the occurence in humans of diseases and/or ailments comprising viral infections; bacterial infections; fungal infections; parastic infections and more specific diseases and/or ailments; such as as, aids; alzheimer's dementia; angiogenesis diseases; aphthour ulcers in AIDS patients; asthma; atopic dermatitis; psoriasis; basal cell carcinoma; benign prostatic hypertrophy; blood substitute; blood substitute in surgery patients; blood substitute in trauma patients; breast cancer; breast cancer; cutaneous & metastatic; cachexia in AIDS; campylobacter infection; cancer; pnemonia; sexually transmitted diseases (STDs); cancer; viral dieases; candida albicians in AIDS and cancer; candidiasis in HIV infection; pain in cancer; pancreatic cancer; parkinson's disease; peritumoral brain edema; postoperative adhesions (prev nt); proliferative diseases; prostate cancer; ragweed allergy; renal dis ase; restenosis;

rheumatoid arthritis; rheumatoid arthritis; allergies; rotavirus infection; scalp psoriasis; septic shock; small-cell lung cancer; solid tumors; stroke; thrombosis; type I diabetes; type I diabetes w/kidney transplants; type II diabetes; viseral leishmaniasis; malaria; periodontal or gum disease; cardiac rthythm disorders; central nervous system diseases; central nervous system disorders; cervical dystonia (spasmodic torticollis); choridal neovascularization; chronic hepatitis c, b and a; colitis associated with antibiotics; colorectal cancer; coronary artery thrombosis; cryptosporidiosis in AIDS; cryptosporidium parvum diarrhea in AIDS; cystic fibrosis; cytomegalovirus disease; depression; social phobias; panic disorder; diabetic complications; disabetic eye disease; diarrhea associated with antibiotics; erectile dysfunction; genital herpes; graft-vs host disease in transplant patients; growth hormone deficiency; head and neck cancer; head trauma; stroke; heparin neutralization after cardiac bypass; hepatocellular carcinoma; HIV; HIV infection; huntington's disease; CNS diseases; hypercholesterolemia; hypertension; inflammation; inflammation and angiogensis; inflammation in cardiopulmonary bypass; influenza; migrain head ache; interstitial cystitis; kaposi's sarcoma; kaposi's sarcoma in AIDS; lung cancer; melanoma; molluscum contagiosum in AIDS; multiple sclerosis; neoplastic meningitis from solid tumors; non-small cell lung cancer; organ transplant rejection; osteoarthritis; rheumatoid arthritis; osteoporosis; drug addiction; shock; ovarian cancer;

Amebiasis; Babesiasis; Chagas' disease (Trypanosoma cruzi); Cryptosporidiosis; Cysticercosis; Fascioliasis; Filariasis; Echinococcosis; Giardiasis; Leishmaniasis; Malaria; Paragonimiasis; Pneumocystosis; Schistosomiasis; Strongylodiasis; Toxocariasis; Toxoplasmosis; Trichinellosis; Trichomoniasis; yeast infection; and pain.

add A2

add A1

TABLE 1

Ampicillin Anhydrate Microcapsules Evaluated in Rats

In Vivo Experiment	Microcapsule Batch	Antibiotic Core Loading, Wt Percent	Microcapsule Dose/ Wound, g (Antibiotic Equivalent, mg)
Efficacy	A382-140-1	18.5	0.50 (92.50)
Dose-Response I	A681-31-1	18.1	0.50 (90.50)
			0.25 (45.25)
			0.10 (18.10)
			0.05 (9.05)
Dose-Response II	B213-66-1S	11.4	0.25 (28.50)
			0.15 (17.10)
			0.05 (5.70)

TABLE 2. Effect of Immediate Antibiotic Therapy for Prevention o Experimental Osteomyelitis in a Rabbit Tibia Model

Group	Treatment	Radiographic Severity[a]	Positive Bone Cultures	Bacterial Counts[b]
A	Parenteral therapy for 14 days	0	0/6	0
B	Microencapsulated ampicillin[c]	0.43 ± 1.13	0/7	0
C	Unencapsulated ampicillin[c]	0	1/4	(±2.3) X 10^2
D	Placebo microcapsules[c]	7.00 ± 0.0	4/4	(±8.3) X 10^6
E	Injection vehicle[c]	6.67 ± 0.58	4/4	(±0.7) X 10^6
F	No treatment	5.25 ± 2.06	5/5	(±4.5) X 10^7

[a] Mean radiographic severity score at 7-weeks post treatment.

[b] Mean (± standard deviation) CFU of S. aureus recovered per gram of bone.

[c] Intramedullary injection.

TABLE 3. Effect of Delayed Therapy without Debridement for Treatment of Experimental Osteomyelitis in a Rabbit Tibia Model

Group	Treatment	Positive Bone Cultures	Bacterial Counts[b]
A	Parenteral therapy for 14 days	6/8	5.9(±16.7) X 10^6
B	Microencapsulated ampicillin[c]	4/8	1.2(±2.2) X 10^3
C	Unencapsulated ampicillin[c]	5/7	2.6(±7.0) X 10^5
D	No treatment	6/6	2.8(±2.9) X 10^5

[a] No statistically significant differences between groups by Chi square analysis (p=0.23)

[b] n (± standard deviation) CFU of *S. aureus* recovered per gram of bone.

[c] ramedullary injection.

TABLE 4. Effect of Delayed Therapy with Debridement for Treatment Experimental Osteomyelitis in a Rabbit Tibia Model

Group	Treatment[a]	Positive Bone Cultures	Bacterial Counts[b]
A	Microencapsulated ampicillin	0/10[c]	0
B	Unencapsulated ampicillin	7/10	$3.3(\pm 4.8) \times 10^2$
C	Placebo microcapsules	5/5	$9.1(\pm 10.9) \times 10^4$
D	Injection vehicle	5/5	$3.7(\pm 4.9) \times 10^5$

a substances were implanted locally into the medullary canal at the time of bridement.

b n (± standard deviation) CFU of S. aureus recovered per gram of bone.

c nificantly different ($p<0.01$) from all other groups by Chi square analysis.

Table 5. Survival of E. coli and S. aureus in rat soft-tissue at 28 days following local or systemic treatment with cefazolin.

Treatment Group (N)	Dose	Mean (±sd) Log CFU/g tissue		Contamination Rate
		E. coli	S. aureus	
A: CZ microspheres (6)	50 mg	1.01 ± 1.59	0.50 ± 1.21	2/6 (33%)
B: CZ microspheres (6)	250 mg	0.91 ± 1.41	0.42 ± 1.04	2/6 (33%)
C: CZ microspheres (6)	500 mg	0	0	0/6 (0%)
D: Free CZ powder (6)	110 mg	0.57 ± 1.40	0.53 ± 1.29	1/6 (17%)
E: Systemic CZ (6)	30 mg/kg	4.44 ± 0.91	0.83 ± 2.03	6/6 (100%)
F: No treatment (3)	0	4.28 ± 0.34	2.12 ± 1.83	3/3 (100%)

Rat wound infection model. Table 5 shows the effect of local versus systemic cefazolin therapy on the contamination rate in rat soft-tissue wounds at 28 days postinfection. Local antibiotic therapy with CZ microspheres, in doses ranging from 50 to 500 mg per wound, was highly effective for eliminating both organisms from the wounds. The maximum effect was achieved in the Group C animals who received the highest dose of CZ microspheres (500 mg) where both E. coli and S. aureus were eliminated from 100% of the wounds. Even at the lowest dose used (50 mg/wound), 4 of 6 wounds were rendered completely sterile. Local antibiotic therapy with free CZ powder sterilized the wounds in 5 of 6 (83%) animals. In contrast, systemic administration of cefazolin (30 mg/kg) failed to sterilize the wounds in any of the 6 Group E animals tested. Chi-square analysis revealed that there was a statistically difference in the frequency of recovery of either E. coli and/or S. aureus (contamination rate) between all groups receiving local antibiotic therapy with CZ microspheres (groups A, B, and C) or free CZ powder (group D) versus the group E animals who received systemic cefazolin therapy ($p < 0.05$). Comparisons of the mean log E. coli counts by analysis of variance showed a statistically significant reduction ($p < 0.01$) for all groups treated by local depot administration of cefazolin (groups A thru D) versus group E (systemic CZ therapy). There were no significant differences, however, in the mean log S. aureus counts among any of the treatment groups ($p > 0.05$).

Table 6. Effect of early antibiotic therapy on infection in S. aureus contaminated rabbit tibial fractures stabilized with internal fixation.

Treatment Group (N)	No. of Animals with: Deep Infection	No. of Animals with: Positive Bone Cultures	Mean (±SD) log bacteria (CFU/g)
A: CZ microspheres (7)	0/7	1/7	0.3 ± 0.9
B. CZ powder (6)	0/6	1/6	0.2 ± 0.5
C. Systemic CZ (5)	3/5	4/5	3.0 ± 2.1
D. Placebo microspheres (3)	3/3	3/3	5.2 ± 0.2
E. No treatment (4)	3/4	4/4	4.2 ± 0.5

Rabbit fracture-fixation model. Table 6 shows the results of the clinical and bacteriological findings at 8 weeks in 25 surviving rabbits when local or systemic antibiotic therapy with cefazolin was initiated within 30 minutes following bacterial contamination of the fractures. Deep infection, defined as the presence of pus on the fixation plate or in the deep tissues, was noted in 6 of the 7 (86%) control animals in Group D (placebo microspheres) and Group E (no treatment). Cultures of the tibiae from all 7 controls were positive for S. aureus. Of the 5 surviving Group C animals who received a 1 week course of systemic cefazolin therapy, deep infection was noted in 3 cases and S. aureus was recovered from the bones of 4 of the 5 animals. In contrast, no clinical evidence of infection was detected in any of the 7 Group A animals who received local antibiotic therapy with CZ microspheres or in the 6 animals in Group B who received an equivalent local dose of free CZ powder. Cultures of the tibiae were sterile in 6 of 7 (86%) Group A and 5 of 6 (83%) Group B animals, respectively. There was a statistically significant difference in the mean log S. aureus counts of the Group A and Group B animals and all other groups by analysis of variance ($p < 0.05$). The mean log S. aureus counts for Group C was also significantly different from all groups with the exception of Group E (no treatment).

Table 7. Effect of delayed antibiotic therapy on infection rates in S. aureus contaminated rabbit tibial fractures.

Treatment Group (N)	No. of Animals with: Deep Infection	Positive Bone Cultures	Mean (±SD) log bacteria (CFU/g)
A: CZ microspheres (8)	0/8	0/8	0
B. CZ powder (8)	4/8	6/8	2.4 ± 1.8
E. No treatment (7)	5/7	7/7	4.3 ± 1.0

Table 7 shows the results of the clinical and bacteriological findings at 8 weeks in 23 surviving rabbits when local antibiotic therapy was delayed for 2 hours following bacterial contamination of the fractures. Clinical evidence of infection was present in 5 of 7 (71%) control animals in Group C and cultures of the tibiae yielded S. aureus in all 7 cases. Of the 8 animals in Group B who received local antibiotic therapy with CZ powder, deep infection was noted in 4 animals and S. aureus was recovered in 6 of 8 (75%) cases. In contrast, none of the 8 animals in Group A (CZ microspheres) developed clinical infections and cultures of the tibiae were sterile in all cases. One way analysis of variance showed a statistically significant difference in the mean log S. aureus counts between Groups A and B ($p = 0.0014$); Groups A and C ($p < 0.0001$); and Groups B and C ($p = 0.0269$).

TABLE 8

Efficacy of Cefazolin Microspheres in Rat Soft Tissue Wounds Contaminated with a Cefazoll-Resistant Strain of S. aureus (MIC = 64 µg/ml)

Treatment Group	Dose	Number of Animals	Number (%) Sterile Wounds
CZ microspheres	500 mg[a]	6	5/6 (83%)
Free CZ powder	110 mg	6	6/6 (100%)
Systemic CZ	30 mg/kg x 7 days	6	0/6 (0%)
Controls	No antibiotics	3[b]	2/2 (0%)

[a] 500 mg of CZ microspheres was applied to the wounds representing 110 mg of cefazolin equivalent

[b] One control animal died during the experiment and no cultures were performed.

LEGEND:

CZ microspheres = Cefazolin-loaded lactide-co-glycolide microspheres

Free CZ powder = Unencapsulated cefazolin powder

Systemic CZ = Intramuscular administration of cefazolin (30 mg/kg/day) given at 8 hour intervals for 7 consecutive days.

Controls = No antibiotic treatment.

Table 15 Microcapsule compositions containing Histatin polypeptide

Composition#	Polymer Description			Theoretical peptide Core Load (%)	Internal Phase Ratio (w/o)	Emulsification Technique
	L/G Ratio & Type	Mol. Wt.(Mw x 10^3)	Conc. in DCM (w/w)			
1.	50/50 ,U	12	38	5	1:20	A
2.	50/50 ,U	12	18.5	2	1:20	A
3.	50/50	34	10	5	1:20	A
4.	50/50 ,U	12	38	5	1:4	A

5.	50/50	34	7	5	1:10	B
6.	50/50	34	10	5	1:10	B
7.	50/50	34	10	5	1:10	A
8.	75/25	12	10	5	1:10	B
9.	75/25	12	23.5	5	1:10	B
10.	50/50	12	10	5	1:10	B
11.	50/50	12	7	5	1:10	B
12.	50/50 ,U	12	10	5	1:10	B
13.	50/50 ,U	12	7	2.3	1:10	B

14.	50/50 ,U	12	10	5	1:10	B
15.	50/50 ,U	34	10	5	1:10	B
16.	50/50 ,U	12	10	5	1:10	B
17.	50/50 ,U	12	20	5	1:10	B
18.	50/50 ,U	12	40	5	1:10	B
19.	50/50 ,U	34	5	5	1:10	B
20.	50/50 ,U	34	10	5	1:10	B
21.	50/50 U	34	15	5	1:10	B

Acronyms:

L/G ratio: Copolymer composition of lactide/glycolide
DCM: Methylene Chloride
Mw: Molecular weight in daltons
A: w/o/w emulsification without an intermediate step for emulsion stabilization
B: w/o/w emulsification with an intermediate step for emulsion stabilization
U: Uncapped polymer